

AMENDMENTS TO THE CLAIMS

Amendments to the claims are reflected in the following listing of claims, which replaces all prior listings and versions of the claims:

1. (Original) A method of screening colon tissue for a pathological condition, said method comprising:

measuring Prox-1 expression in a biological sample that comprises colon tissue from a mammalian subject, wherein elevated Prox-1 expression in the colon tissue correlates with a pathological phenotype.

2. (Original) A method according to claim 1, comprising comparing Prox-1 expression in the colon tissue to Prox-1 expression in healthy colon tissue, wherein increased Prox-1 expression in the colon tissue from the mammalian subject correlates with a pathological phenotype.

3. (Currently amended) A method according to claim ~~[[1 or]]~~ 2, further comprising a step, prior to said measuring step, of obtaining the biological sample comprising colon tissue from a mammalian subject.

4. (Currently amended) The method according to claim 1 ~~any one of claims 1-3~~, wherein the pathological condition is colon cancer, and wherein increased Prox-1 expression in the colon tissue is indicative of a cancerous or precancerous condition.

5. (Currently amended) The method according to claim 1 ~~any one of claims 1-4~~, wherein the measuring comprises measuring Prox-1 protein in the biological sample.

6. (Original) The method of claim 5, wherein the measuring comprises contacting the colon tissue with a Prox-1 antibody or antigen-binding fragment thereof.

7. (Currently amended) The method of claim 1 ~~any one of claims 1-6~~, wherein the measuring comprises measuring Prox-1 mRNA in the colon tissue.

8. (Original) The method of claim 7, wherein the measuring comprises *in situ* hybridization to measure Prox-1 mRNA in the colon sample.

9. (Original) The method of claim 7, wherein the measuring comprises steps of isolating mRNA from the colon tissue and measuring Prox-1 mRNA in the isolated mRNA.

10. (Currently amended) The method according to claim 1 ~~any one of claims 1-9~~, wherein the measuring comprises quantitative polymerase chain reaction (PCR) to quantify Prox-1 mRNA in the colon tissue relative to Prox-1 mRNA in healthy colon tissue.

11. (Currently amended) A method according to claim 1 ~~any one of claims 1-10~~, further comprising measuring expression of at least one gene selected from the group consisting of CD44, Enc1, and ID2 in the colon tissue, wherein elevated Prox-1 expression and elevated expression of the at least one gene in the colon tissue correlate with a pathological phenotype.

12. (Currently amended) A method according to claim 1 ~~any one of claims 1-11~~, further comprising measuring activation of β -catenin/TCF pathway in the colon tissue, wherein activation of the β -catenin/TCF pathway and elevated Prox-1 expression in the colon tissue correlate with a pathological phenotype.

13. (Original) A method according to claim 12, wherein activation of the β -catenin/TCF pathway is measured by at least one indicator in the colon tissue selected from the group consisting of: mutations in an APC gene; mutations in a β -catenin gene; and nuclear localization of β -catenin.

14. (Currently amended) The method according to claim 1 ~~any one of claims 1-13~~, wherein the mammalian subject is a human.

15. (Original) A method according to claim 14, further comprising a step of administering to a human subject identified as having a pathological condition characterized by increased Prox-1 expression in colon tissue a composition comprising a Prox-1 inhibitor.

16. (Canceled).

17. (Original) A method of inhibiting the growth of colorectal cancer cells in a mammalian subject comprising the step of:

administering to the subject a composition comprising a molecule that suppresses expression or activity of Prox-1, thereby inhibiting the growth of colon carcinoma cells.

18. (Canceled).

19. (Canceled).

20. (Canceled).

21. (Currently amended) The method ~~or use~~ according to claim 17 ~~any one of claims 16-20~~, wherein the composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

22. (Currently amended) The method ~~or use~~ according to claim 17 ~~any one of claims 16-21~~, wherein the molecule comprises a nucleic acid selected from the group consisting of an antisense oligonucleotide that inhibits Prox-1 expression; micro-RNA that inhibits Prox-1 expression; short interfering RNA (siRNA) that inhibits Prox-1 expression; and short hairpin RNA (shRNA) that inhibits Prox-1 expression.

23. (Canceled).

24. (Canceled).

25. (Currently amended) The method or use of claim 22, ~~[[24,]]~~ wherein the siRNA comprises at least one nucleotide sequence set forth in SEQ ID NOS: 4, 5, 6, and 7.

26. (Currently amended) The method of claim 17 ~~or use according to any one of claims 16-21~~, wherein the molecule comprises a zinc finger protein that inhibits Prox-1 expression.

27. (Currently amended) The method of claim 17 ~~or use according to any one of claims 16-21~~, wherein the molecule comprises a dominant negative form of Prox-1

protein, or an expression vector containing a nucleotide sequence encoding the dominant negative Prox-1 protein.

28. (Original) The method or use of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted DNA binding domain.

29. (Original) The method or use of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted transactivation domain.

30. (Canceled).

31. (Currently amended) The method according to claim 17 ~~any one of claims 17-30~~, wherein the composition is administered in an amount effective to suppress Prox-1 expression and increase Notch 1 signaling.

32. (Canceled).

33. (Currently amended) The method according to claim 17 ~~any one of claims 17-31~~, wherein the composition is administered in and amount effective to increase 15-PDGH activity or decrease prostaglandin D2 synthase activity.

34. (Currently amended) The method according to claim 17 ~~any one of claims 17-31~~, further comprising administering to the subject an inhibitor of the β -catenin/TCF signaling pathway.

35. (Canceled).

36. (Currently amended) The method of claim 34 ~~or use of claim 34 or 35~~, wherein the inhibitor of the β -catenin/TCF signaling pathway is dominant negative form of TCF-4.

37. (Currently amended) The method of claim 34 ~~or use of claim 34 or 35~~, wherein the inhibitor of the β -catenin/TCF signaling pathway targets TCF-4, β -catenin, or c-myc.

38. (Currently amended) The method of claim 17 ~~according to any one of claims 17-31~~, further comprising administering to the subject a COX-2 inhibitor.

39. (Canceled).

40. (Canceled).

41. (Currently amended) The method of claim 17 ~~according to any one of claims 17-31~~, further comprising administering to the subject a Notch signaling pathway agonist.

42. (Canceled).

43. (Canceled).

44. (Canceled).

45. (Canceled).

46. (Original) A method of inhibiting Prox-1 function in a mammalian subject having a disease characterized by Prox-1 overexpression in cells, comprising the step of administering to said mammalian subject a composition, said composition comprising a compound effective to inhibit Prox-1 function in cells.

47. (Canceled).

48. (Original) A method of screening for a Prox-1 modulator, comprising steps of:

contacting a test molecule with Prox-1 protein, or a nucleic acid comprising a nucleotide sequence that encodes Prox-1 protein, under conditions which permit the interaction of the test molecule with the Prox-1 protein or nucleic acid;

and measuring interaction between the test molecule and Prox-1 protein or nucleic acid, wherein a test molecule that binds the Prox-1 protein or nucleic acid is identified as a Prox-1 modulator.

49. (Canceled).

50. (Canceled).

51. (Canceled).

52. (Original) A method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of:

a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound;

b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the DNA and the Prox-1 protein in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

53. (Canceled).

54. (Currently amended) A method according to claim 48 ~~any one of claims 48-53~~, further comprising steps of:

contacting a cell from a colorectal cancer or colorectal cancer cell line with the Prox-1 modulator; and

selecting a Prox-1 modulator that inhibits growth of the cell.

55. (Original) A method according to claim 54, further comprising:

formulating a composition comprising the selected Prox-1 modulator and a pharmaceutically acceptable carrier;

administering the composition to a mammalian subject having a colorectal cancer; and

monitoring the mammalian subject for growth, metastasis, shrinkage, or disappearance of the colorectal cancer.

56. (Canceled).

57. (Canceled).

58. (Canceled).

59. (Canceled).

60. (Canceled).

61. (Canceled).

62. (Canceled).

63. (Canceled).

64. (Canceled).

65. (Canceled).

66. (Canceled).

67. (Canceled).

68. (Currently amended) The method of claim 17 ~~use according to claim 16~~, wherein the molecule comprises a compound comprising a nucleic acid 8 to 50 nucleotides in length, wherein said compound specifically hybridizes with a polynucleotide encoding Prox-1, or hybridizes to the complement of the polynucleotide, and inhibits the expression of Prox-1 when introduced into a cell that expresses Prox-1.

69. (Canceled).

70. (Currently amended) The method of claim 22 ~~use of claim 69~~, wherein the antisense oligonucleotide has a sequence complementary to a fragment of SEQ ID NO: 1.

71. (Currently amended) The method ~~use~~ of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a promoter or other control region, an exon, an intron, or an exon-intron boundary.

72. (Currently amended) The method ~~use~~ of claim 70, wherein the fragment of SEQ ID NO: 1 comprises an exon-intron splice junction.

73. (Currently amended) The method ~~use~~ of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a region within 50-200 bases of an exon-intron splice junction.

74. (Currently amended) The method of claim 17 ~~or use according to any one of claims 16-21~~, wherein the molecule comprises an inhibitor of DNA methyltransferases, thereby inhibiting Prox-1 expression.

75. (Currently amended) The method ~~or use~~ according to claim 74, wherein the inhibitor of DNA methyltransferases is 5-aza-2'-deoxycytidine.

76. (Currently amended) The method according to claim 22 ~~any one of claims 22-31~~, further comprising administering to the subject an inhibitor of DNA methyltransferases.

77. (Canceled).

78. (Canceled).